Received: 27 May 2020 | Revised: 12 November 2020 | Accepted: 16 December 2020

DOI: 10.1002/ccr3.3832

CASE REPORT

Clinical Case Reports Open Access WILEY

Clinical cases of amyotrophic lateral sclerosis concurrent with hydromyelia

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Funding information
This study was funded by a grant #19-15-00329 of the Russian Science Foundation.

Abstract

A comprehensive work-up, clinical correlation, and differential diagnosis are needed to determine if abnormal findings such us hydromyelia in ALS patients are causative or incidental in order to rule out other, more curable conditions that resemble ALS.

KEYWORDS

amyotrophic lateral sclerosis, hydromyelia, Motor neuron disease, MRI, spinal cord, syringomyelia

1 | INTRODUCTION

In this report, we present two clinical cases of ALS accompanied by incidentally detected hydromyelia. We tried to determine the causes of cavities and their connection with the disease. After a diagnostic work-up of patients, these cavities did not appear to have a causative relationship with the disease.

Amyotrophic lateral sclerosis is a progressive fatal neurodegenerative disease that affects upper and lower motor neurons. The disease begins with a focal weakness and gradually spreads to affect most muscles, including the diaphragm. Usually, death occurs due to respiratory failure within 3 to 5 years of diagnosis.[1] Despite extensive research on ALS biomarkers, the diagnosis is based on clinical presentation and supported by EMG results.[2] MRI is used in the diagnosis of ALS to exclude the possibility of other diseases.

The patient in Case 1 is a 36-year-old man with a six-year history of ALS accompanied by an accidentally revealed slitlike syrinx cavity that looked like a dilated central canal of the thoracic spinal cord. Case 2 is a 61-year-old female patient with ALS and dilated central canal of the cervical spinal cord. In both cases, after an MRI scan, patients were diagnosed with hydromyelia even before they developed any typical clinical symptoms of ALS, which was the cause of the delay and difficulty in making accurate diagnosis. In this paper, we discuss the differential diagnosis, consider the possible causes of the central canal dilation, and discuss whether the abnormal findings are causative or incidental in the presented cases.

2 | CASE 1 HISTORY, EXAMINATION

In 2013, a 30-year-old male patient developed cramps in the right calf muscle. By 2014, the patient developed right leg weakness, fasciculation in right leg muscles, wasting of the right leg anterior compartment, and right foot drop. At the time, the neurological examination results showed the

muscle strength of 5/5 points in the left limbs and 5/5 points in the right limbs with the exception of the extensors where the strength of 2/5 points was assessed; it also revealed the amyotrophy of the right leg anterior compartment muscles, and absence of sensation disturbances (Figure 1). Disease progression was slow, and by 2015, amyotrophy developed in the right thigh muscles. By the end of 2015, the patient had fasciculations throughout the body, painful cramps and muscle weakness in the left shin. During that time, the examination revealed brisk knee reflexes, and the positive Babinski sign on the right side. The patient developed his left leg amyotrophy with a foot drop by 2016. In 2018, muscle weakness spread to his left thigh and upper extremities.

The patient was observed over the period of time, and in 2019, neurological assessment revealed restricted movements, mostly in lower limbs, excessive amyotrophy of the right and left legs, but no observable amyotrophy of the upper limbs (Figure 2). Generalized fasciculations were noted. Motor examination showed significant muscle weakness of the lower limbs more prominent in distal part, and mild weakness of the upper limbs. Deep tendon reflexes were brisk with wide spread, except Achilles reflex, which was absent on both sides. Hoffmann sign was positive, and Babinski sign was negative on the right and left side. Sensation in all dermatomes to pinprick, temperature, vibration, and proprioception were normal. There were no speech, swallowing, or breathe disturbances.

Over the course of the disease, the patient underwent MRI and EMG examinations. In 2015, MRI of the thoracic spinal cord showed slitlike syrinx cavity that looked like a dilated central canal of the thoracic spinal cord at the ThIII – ThIXvertebrae level, no Chiari malformation or other extramedullary factors associated with the development of syringomyelia were found (Figure 3). MRI of the brain and cervical spine revealed no pathology. In 2015, EMG showed signs of damage to the lower motor neurons of the lumbar and cervical levels of the spinal cord, including abnormal spontaneous activity (fibrillation potentials, fasciculations), large amplitude and long duration motor unit potentials both in upper and lower limbs, and no conduction blocks. In 2016, EMG showed that these abnormalities became more significant. Follow-up MRI in both 2016 and 2019 showed no significant changes in cavity size (Figure 4). In addition, the patient underwent testing for titer of GM-1 and GM-2 antibodies (markers of multifocal motor neuropathy), which were negative. Other laboratory tests of blood and CSF were normal. Unfortunately, genetic testing was not available.

3 | DISCUSSION

The patient's initial neurological syndrome was hypotrophy of the right leg. The initial diagnoses were as follows: monomelic amyotrophy (MMA), spinal muscular atrophy (SMA), progressive muscular atrophy (PMA), and multifocal motor neuropathy (MMN). MMA was characterized by the signs of spinal cord atrophy and vertebral canal stenosis, which were not detected by MRI, as well as the absence of sensitive disturbances.[3] SMA was characterized by symmetrical amyotrophy; however, the patient experienced long-term amyotrophy and muscle weakness only in his right leg. EMG revealed no conduction blocks, and the titers of GM-1 and GM-2 antibodies were not detected, which made it possible to eliminate the

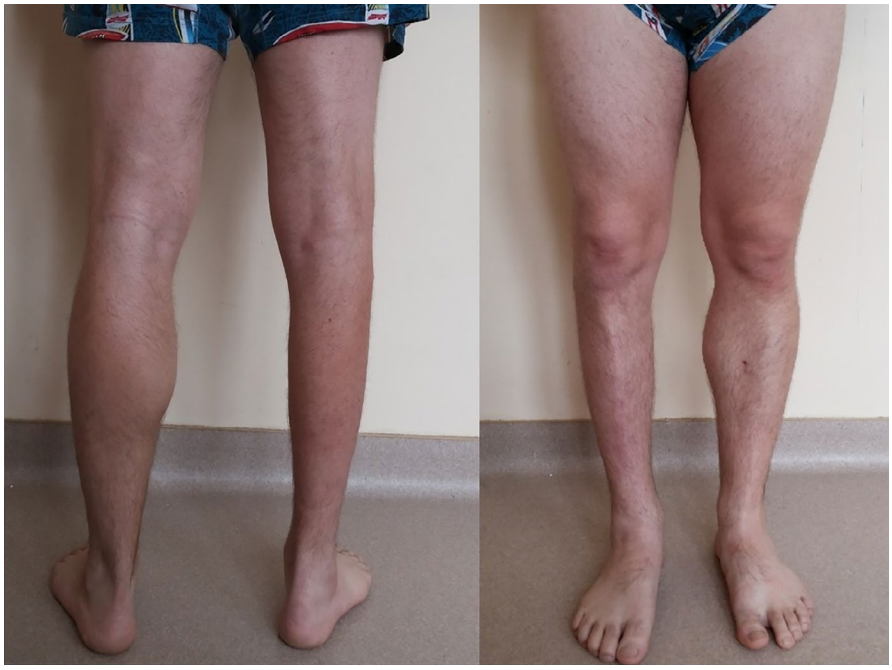

FIGURE 1 2015, hypotrophy of the only right leg muscles, most prominent in distal part

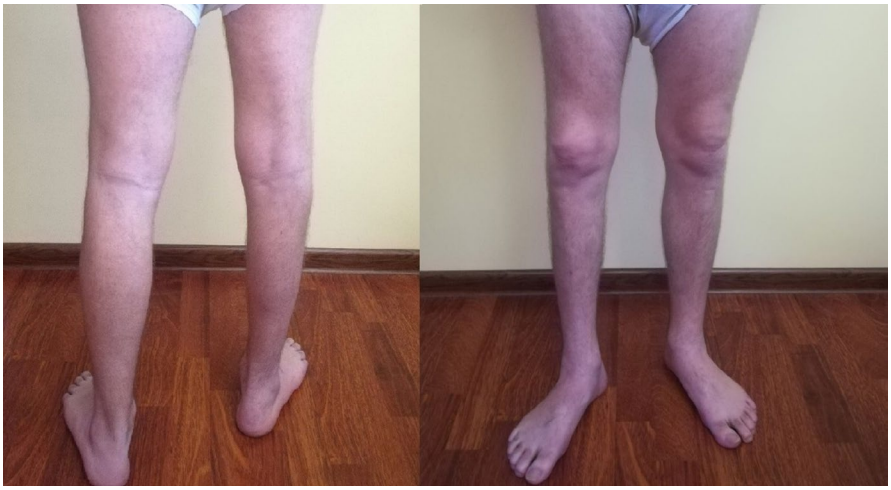

FIGURE 2 2019, hypotrophy involved the left leg muscles

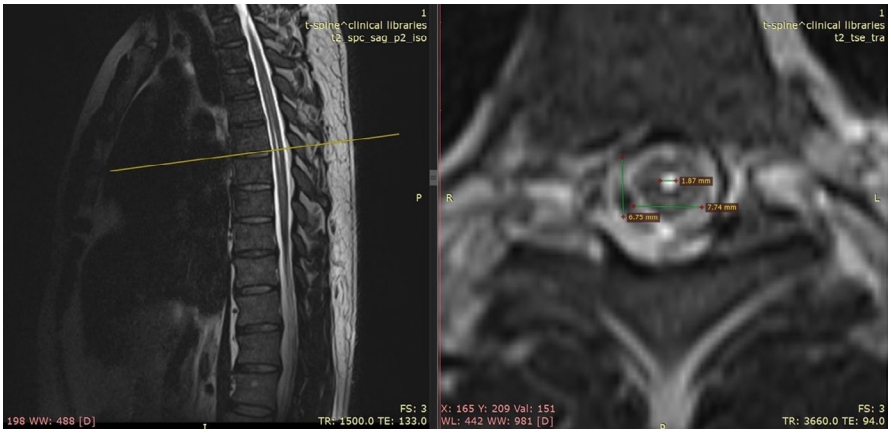

FIGURE 3 2015, T2-weighted MRI of thoracic spine, anteroposterior size 6.75 mm, width 7.74 mm, cavity size 1.87 mm (anteroposterior size and width lines are offset to avoid overlapping)

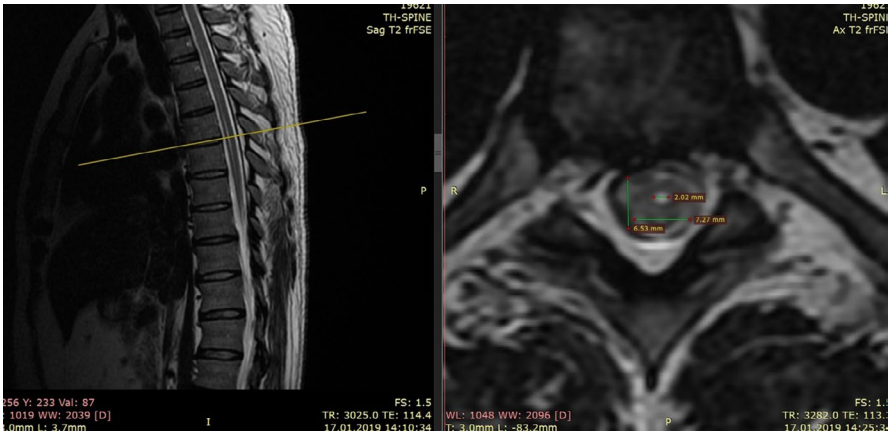

FIGURE 4 2019, T2-weighted MRI of thoracic spine, anteroposterior size 6.53 mm, width 7.27 mm, cavity size 2.02 mm (anteroposterior size and width lines are offset to avoid overlapping)

possibility of MMN.[4] As the disease progressed, symptoms of upper motor neuron damage developed, such as brisk reflexes and pathological signs. EMG showed signs of damage to the motor neurons of the anterior horns of the spinal cord in the segments outside the affected right leg. Finally, in 2015, the combination of lower and upper motor neuron (LMN and UMN) clinical signs of one lumbar region, EMG LMN signs in lumbar and cervic regions, made it possible to diagnose a clinically probable laboratory supported ALS according to the revised El-Escorial criteria concurrent with hydromyelia.[2] In 2019, the diagnosis was changed to possible ALS.

We examined whether the revealed central canal dilation has a clinical manifestation in this patient. Our clinical

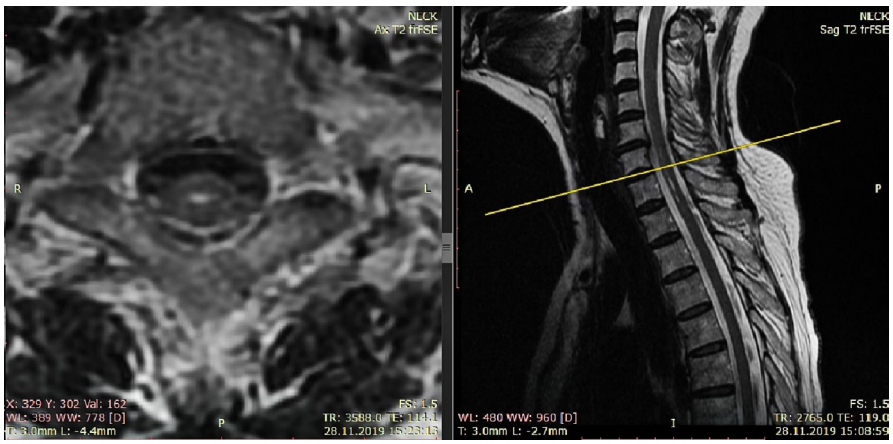

FIGURE 5 2019, T2-weighted MRI shows dilated central canal at the C6-Th1 vertebrae level and slightly narrow of vertebral canal (vertebral canal is less than vertebrae's front-rear size). (Unfortunately the patient was unable to provide previous MRI from 2014 and 2018)

experience allowed us to claim that the dilation of the central canal of such small diameter without increasing over time cannot cause progressive severe paresis and amyotrophy of the lower limb.[5]

The reason for the central canal dilation is unclear. The MRI showed no Chiari malformation or other extramedullary factors associated with the development of syringomyelia. In addition, there was no history of spinal cord trauma, inflammatory processes, infarction or hemorrhage. We suppose that the presence of hydromyelia is a casual association. For example, Holly and Betzdorf (2002) argued, that slitlike syrinx cavities are remnants of the central canal and can be found in a small percentage of adults.[6] Patients with slitlike syrinx could be neurologically intact or just report the pain in different distributions. A study by Petit-Lacour et al (2000) demonstrated that 1.5% of MRI scans show an asymptomatic slitlike syrinx.[7] Follow-up imaging revealed no changes in cavity size.

However, some authors report the cases of neurodegenerative diseases concurrent with hydromyelia. In one case, Masciullo et al (2016) described a patient with SPG56 – rare form of hereditary spastic paraplegia, caused by mutations in CYP2U1 and concurrent with hydromyelia.[8] The authors proposed that the presence of hydromyelia is not a casual association, but it may be part of the phenotype of SPG56. The authors supposed the hydromyelia in these cases is linked to mitochondrial dysfunction. It is supported by the cases of hydromyelia described in patients with Charcot-Marie-Tooth disease 2A-type (CMT2A) and harboring mutations in MFN2.[9] In the study of Bombelli F. et al, the involvement of the CNS in the pathological process has been found in these patients with CMT2A: 26% of patients had CM abnormalities, 9% of patients had hydromyelia. The authors also believe that the spinal cord cavity in these patients is not a coincidence, but a part of the phenotype. Both CYP2U1 and MFN2 encode enzymes regulating energy metabolism and mitochondrial dynamics. In recent ALS reviews, mitochondrial dysfunction was indicated as one of the pathogenic links.[10]

4 | CASE 2 HISTORY, EXAMINATION

A 61-year-old female patient was admitted to our neurology department in 2019. Patient's complaints included progressive muscle spasticity and weakness, more prominent in lower limbs, muscle hypotrophy, and speaking and swallowing disturbances. First symptoms were developed in 2012 when patient noticed walking difficulty due to spasticity and weakness in the right leg. In 3 months, muscle weakness involved the left leg. The disease slowly progressed, and the patient started using a walking stick by 2014, and a wheelchair by 2016. In 2014, the patient developed hypotrophy of the interosseous muscles of the hands and thenar hypotrophy. From 2012 to 2018, the disease progressed slowly, the symptoms only included increasing muscle weakness of lower limbs and spasticity. During 2014-2016, the patient had urge incontinence. In 2018, the patient experienced muscle weakness in the right hand, in 2019, she developed muscle weakness in the left hand and bulbar muscles (dysphonia, dysphagia).

In 2019, a neurological examination revealed tetraparesis with severe muscle weakness in lower limbs up to 2/5 points and mild weakness in upper limbs up to 4/5 points. The patient was not able to stand or walk by herself. Tendon reflexes were brisk and wide spread. Rare fasciculations in limbs, pronounced tongue fasciculations, moderate muscle hypotrophy of all limbs, speaking and swallowing disturbances, Hoffmann and Babinski signs, and spasticity more prominent in lower limbs were developed. There were no sensation disturbances.

Over the course of the disease, the patient underwent MRI several times, as well as EMG and TMS. In 2012-2013, MRI of the lumbar spine revealed no pathology of the spinal cord. In 2014, MRI of the cervic and thoracic spine revealed adilated central canal at the C6-Th1 vertebrae level and slightly narrow vertebral canal (vertebral canal is smaller than vertebrae's front-rear size). The spinal cord anterior horns damage signs in the form of both motor unit remodeling and

denervation were revealed by EMG in 2014 and 2015, including chronic denervation-reinnervation, large amplitude and long duration motor unit potentials, abnormal spontaneous activity of motor fibers such as fibrillation potentials and fasciculations. Moreover, in 2015, TMS showed a motor pathway dysfunction at the cortical level. In 2019, dilated central canal of the cervical spinal cord remained the same size (C6-Th1) according to MRI (Figure 5). Laboratory tests of blood and CSF were normal.

5 | DISCUSSION

Case 2 corroborates the clinical Case 1of a 36-year-old male patient suffering from ALS with a dilated central canal of the thoracic spinal cord. Both clinical cases share some common features, such as the slow progression of the disease, manifestation in the lower limbs and presence of a cavity in the spinal cord. At the same time, these cases differ from each other by their initial main syndrome. In Case 1, the initial syndrome was lower monoparesis with the amyotrophy, whereas, in Case 2, spastic lower paraparesis was the initial syndrome. Spastic paraparesis is a wide group of pathologies, including spondylogenic myelopathy, demyelinating disorders (multiple sclerosis, neuromyelitis optica), vascular diseases (spinal cord infarction, arteriovenous shunts), and neurodegenerative diseases (hereditary spastic paraplegia, primary lateral sclerosis), etc.[11] The probability of spondylogenic myelopathy, demyelinating, and vascular disorders was excluded after the brain and the spinal cord MRI did not show any typical signs of these disorders. Our patient had symptoms (spastic paraparesis and urinary urgency) consistent with uncomplicated hereditary spastic paraplegia (HSP) except for sensory signs. Primary lateral sclerosis (PLS) is the diagnosis of exclusion characterized by the clinical presence of upper motor dysfunction, most commonly in the legs, in the absence of sensory signs, marked fasciculation and muscle atrophy. EMG is usually normal, but can reveal minimal denervation that does not fulfill El Escorial criteria.[12]

Our patient developed notable limbs amyotrophy, marked tongue fasciculation, and EMG data met El Escorial criteria, therefore HSP and PLS were excluded. Given all the data in 2015, clinically probable laboratory supported ALS was diagnosed according to revised El Escorial criteria.[2] It was changed to possible ALS in 2017 and definite ALS in 2019.

In this case, the question of the cause of the cavity arises. In Case 1, we concluded that the condition occurred at random. This patient had signs of narrowing of the spinal canal on MRI (size of vertebral canal is less than vertebrae's front-rear size). There was no history of the spinal cord damage. Therefore, we hypothesize that a slightly narrow vertebral canal is the cause of the central canal dilation, and this cavity can be classified as noncommunicating central canal dilation.[13] Moreover, such small cavity does not have a contribution in clinical manifestation. During 2014-2019, the cavity remained same size, despite the dramatic clinical deterioration in the last 2 years.

Two previously published case reports described cervical syringomyelia concurrent with ALS. In one case, an autopsy revealed 4 independent syrinxes located between C2-C7, one of them was considered to be idiopathic syringomyelia, others were caused by cervical spondylosis, but relationship between ALS and the syrinxes was not indicated.[14] The other case report described a patient with bulbar-onset ALS and Klippel-Feil syndrome with asymptomatic cervical syringomyelia. After a diagnostic work-up the cervical syringomyelia was excluded as the cause of the symptoms observed in the patient. Clinical signs of the upper and lower motor neuron deficits in the cervical, thoracic, and lumbar regions supported by the results of electrophysiological and biochemical testing led to a diagnosis of ALS.[15]

Therefore, it can be concluded that this is a very rare combination. Taking into account the fact that hydromyelia is a phenotypic feature of some neurodegenerative diseases,[8,9] there is a possibility that hydromyelia may be a part of the phenotype in the rare cases of ALS.

We have come to a conclusion, that in presented cases the abnormalities could be incidental. This might not be the case in other instances, therefore, it is important for clinicians to be aware of abnormal findings that may or may not be causative and should be thoroughly examined to rule out ALS mimicking diseases, some of which could be curable.

ACKNOWLEDGMENTS
Published with written consent of the patients.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
EI Bogdanov, EG Mendelevich, AN Khabibrakhmanov, GR Mukhamedzhanova were attending doctors in Case 1. EI Bogdanov, AN Khabibrakhmanov were attending doctors in Case 2. EI Bogdanov and EG Mendelevich conceived the study. GR Mukhamedzhanova collected Case 1 data in 2015 - 2016. AN Khabibrakhmanov collected Case 1 and 2 data in 2019, prepared the original draft. EI Bogdanov, S.E Bogdanov, and MA Mukhamedyarov – draft review and editing, instrumental data analyzing. All authors read and approved the final manuscript.

ETHICAL APPROVAL
This study was approved by the Local Ethic Committee of the Kazan State Medical University. The patients gave informed written consent to publish de-identified information and clinical and radiographic images.

DATA AVAILABILITY STATEMENT

Data sharing was not applicable to this article as no datasets were generated or analyzed in the production of the manuscript.

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How to cite this article: Bogdanov EI, Mendelevich EG, Khabibrakhmanov AN, Bogdanov SE, Mukhamedzhanova GR, Mukhamedyarov MM. Clinical cases of amyotrophic lateral sclerosis concurrent with hydromyelia. *Clin Case Rep*. 2021;9:1571–1576. https://doi.org/10.1002/ccr3.3832